UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/646,063 | 08/22/2003 | Martin H. Teicher | 04843/113003 | 8435 |

21559 7590 05/04/2009

CLARK & ELBING LLP
101 FEDERAL STREET
BOSTON, MA 02110

| EXAMINER | |
|---|---|
| CORDERO GARCIA, MARCELA M | |
| ART UNIT | PAPER NUMBER |
| 1654 | |

| NOTIFICATION DATE | DELIVERY MODE |
|---|---|
| 05/04/2009 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/646,063 | TEICHER ET AL. | |
| | Examiner | Art Unit | |
| | MARCELA M. CORDERO GARCIA | 1654 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *17 February 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *12, 14-15,22-25, 28-37* is/are pending in the application.

4a) Of the above claim(s) *24 and 34-37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12, 14-15, 22-23, 25, 28-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 17 February 2009 has been entered.

Any rejection from the previous office action, which is not restated here, is withdrawn.

In the Office Action dated 31 March 2005, Examiner stated that the elected species drawn to polyguanidyl conjugate of Example 3, the structure of which is provided in page 30 of the specification, was free of the prior art. Although this is still deemed correct, please note that there are generic claims drawn to polyguanidyl conjugates which are still not deemed free of the prior art as set forth below.

Claims 12, 14-15, 22-25, 28-37 are pending in the application. Claim 12 was amended by Applicant. Claims 12, 14-15, 22-25, 28-37 are presented for examination on the merits. Claims 12, 14-15, 22-23, 25, 28-33 are drawn to the examined species. Claims 24, 34-37 are withdrawn as not drawn to the elected species.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12, 14-15, 22-25, 28-37 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

**New Matter**

The claims have been amended (cf. amendment filed 2/17/09) as follows:

(a) said corticosteroid and said linker are connected via a first linkage group, and (b) said linker and said bulky group are connected via a second linkage group, each of said first linkage group and said second linkage group selected, independently, from an amine, amide, hydrazide or thioether linkage;

The original claim contains a linker defined by formula IIII as in page 3 of claim 12. Applicant has now amended the claims in page 4 of claim 12 to encompass 2 linkages: a first linkage linking linker and corticosteroid; and a second linkage linking linker and bulky group. The linkages are amine, amide, hydrazide and thioether linkage. Applicants have stated that no new matter was introduced and have provided the following support: "[s]pecification from page 14, line 7, to page 18, line 13. Amine linkage groups are described in the specification at page 15, lines 26-28 and at page 15, lines 19-23, and at page 15, lines 16-18. Amide linkage groups are described in the specification from page 16, line 12, to page 17, line 8, and in Examples 2, 3, 6 and 7. Hydrazide linkage groups are described in the specification at page 16, lines 20-24, and

in Example 4 and 5. Thioether linkage groups are described in the specification at page 15, lines 3-12.

***Lack of Ipsis Verbis Support***

The specification is void of any support that would clearly support the instant amendment. The specification teaches "Most commonly, however, the linker will include two or more reactive moieties, as described above, connected by a spacer element. The presence of such a spacer permits bifunctional linkers to react with specific functional groups within the corticosteroid and the bulky or charged group, resulting in a covalent linkage between the two. The reactive moieties in a linker may be the same (homobifunctional linker) or different (heterobifunctional linker, or, where several dissimilar reactive moieties are present, heteromultifunctional linker), providing a diversity of potential reagents that may bring about covalent attachment between the corticosteroid and the bulky or charged group." ([0077] in the instant application's publication). However, the instantly claimed (a) said corticosteroid and said linker are connected via a first linkage group, and (b) said linker and said bulky group are connected via a second linkage group, each of said first linkage group and said second linkage group selected, independently, from an amine, amide, hydrazide or thioether linkage; are not expressly described in the specification or originally filed claims.

***Lack of Inherent Support***

"While there is no in haec verba requirement, newly added claim limitations must be supported in the specification through express, implicit, or inherent disclosure." See MPEP 2163. Based on the disclosure including the few examples provided as support

for amide and hydrazide linkages (Examples 2-7) and listing of amine and thioether bonds is not enough deemed enough guidance/support to carve out a sub-genus from amongst the original genus comprising linkages both to the corticosteroid and to the bulky group, i.e., *independently selected from amine, amide, hydrazide or thioether* for all the corticosteroid conjugates encompassed by the instant claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 12, 14-15, 22-25, 28-37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 12 is drawn to conjugates “being resistant to in vivo cleavage, such that in vivo less than 10% of the administered corticosteroid conjugate is cleaved, separating said corticosteroid from said group, prior to excretion”. The term "10%" in claim 12 is a relative term which renders the claim indefinite. The term "excretion" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. For example, it is not clear whether the excretion is *total* excretion or how it is measured. Claims 31 and 32 are drawn to similar limitations (5% and 2%) also deemed vague and indefinite for the same reasons.

Additionally, the original claim contains a linker defined by formula IIII as in page 3 of claim 12. Applicant has now amended the claims in page 4 of claim 12 to encompass 2 linkers: a first linkage group and a second linkage group. It is not clear

how the linkages relate to the linker and if they are encompassed by the linker as originally filed or if they are extra appendages to the linker.

Dependent claims are also rejected for the reasons set forth above.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

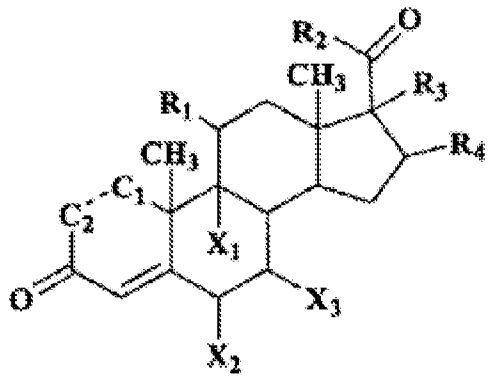
> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1-23, 25, 31-33 rejected under 35 U.S.C. 102 (b) as being anticipated by Rothbard et al. (US 2002/0127198).

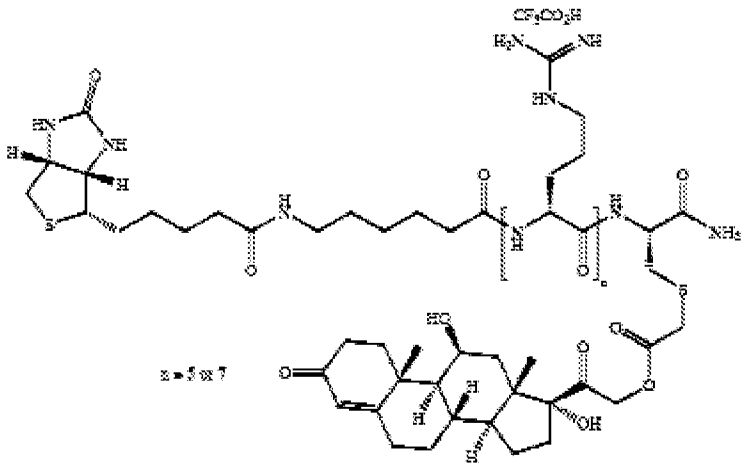
Rothbard et al. teach a method of treating for therapeutic purposes a mammal suffering from an autoimmune or inflammatory condition (e.g., [0203]), said method comprising administering to said mammal a corticosteroid conjugate comprising a

corticosteroid attached via a linker a bulky group of greater than 400 daltons in an amount effective to treat said condition, wherein said corticosteroid is described by formula I




I

wherein the bond between C1 and C2 is a single bond, X1, X2 and X3 represent H, :R1 is OH; R2 is CH2OG1; G1 is a bond between said corticosteroid and said linker; wherein said linker is described by formula III G1-R10-G2, o, p, s, t, u and v are each 0, R10 is a branched heteroalkyl of 9 atoms, G2 is a bond between said linker and said bulky group, R3 is OH and R4 is H; and (a) said corticosteroid and said linker are connected via a first linkage group, and (b) said linker and said bulky group are connected via a second linkage group selected, independently, from an amine, amide, hydrazide, or thioether linkage; and wherein said condition is selected from



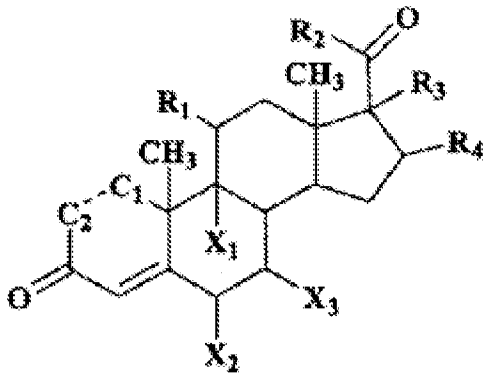
See, e.g., Example 10, page 26; Example 22, pages 40-41. [0203] teaches that conjugated glucocorticoids such as hydrocortisone, prednisone and prednisolone are used to treat eczema (including atopic dermatitis, contact dermatitis, allergic dermatitis), exfoliative dermatitis, lupus, allergic rhinitis ([0223]), Sjogren's disease ([0234]), rheumatoid arthritis ([0213]) and the like. See also [0019], [0076]. The limitation "said corticosteroid conjugate (i) having anti-inflammatory activity in vivo, (ii) having reduced activity in the central nervous system in comparison to said corticosteroid without said group, and (iii) being resistant to in vivo cleavage, such that in vivo less than 10% of the administered corticosteroid conjugate is cleaved, separating said corticosteroid from said group, prior to excretion" necessarily reads upon the compounds taught by Rothbard et al. because the compounds taught (e.g., Example 10 and Example 22, pages 40-41) anticipate every single structural limitation in the claim as set forth above. The limitation "polyguanidino" is taught, e.g., in claim 1 of Rothbard et al., which teaches 5-50 subunits of guanidino molecules in the delivery-enhancing conjugates. See also claims 6, 12, 13, 32 and 37, drawn to specific linkers for the conjugates. The limitation

"rheumatoid arthritis" is taught, e.g., in [0213]. With regards to half life, cols 18-19 teach that it may take up to 24 hours for half the administered compound to dissociate in vivo (e.g., in [0149]). See pages 12-15 for linkers which encompass amino, amide, thiol.

Therefore, the reference is deemed to anticipate the claims above, as drafted.

Claims 1-23, 25, 31-33 are rejected under 35 U.S.C. 102 (e) as being anticipated by Rothbard et al. (US 6,593,292).

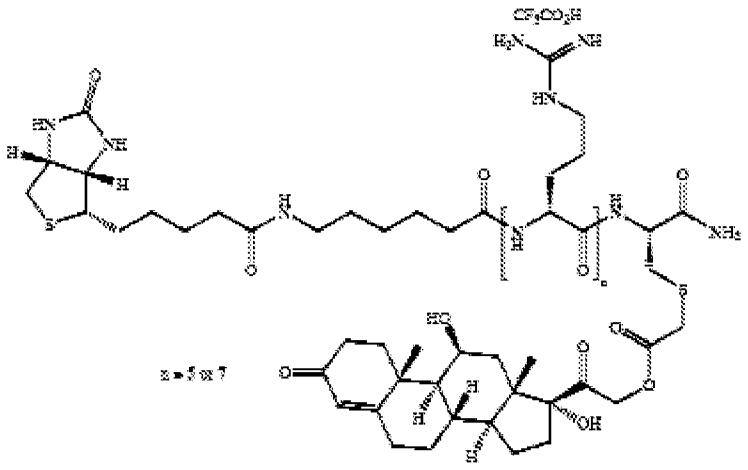
Rothbard et al. teach a method of treating for therapeutic purposes a mammal suffering from an autoimmune or inflammatory condition (e.g., [0203]), said method comprising administering to said mammal a corticosteroid conjugate comprising a corticosteroid attached via a linker a bulky group of greater than 400 daltons in an amount effective to treat said condition, wherein said corticosteroid is described by formula I




I

wherein the bond between C1 and C2 is a single bond, X1, X2 and X3 represent H, :R1 is OH; R2 is CH2OG1; G1 is a bond between said corticosteroid and said linker;

wherein said linker is described by formula III G1-R10-G2, o, p, s, t, u and v are each 0, R10 is a branched heteroalkyl of 9 atoms, G2 is a bond between said linker and said bulky group, R3 is OH and R4 is H; and (a) said corticosteroid and said linker are connected via a first linkage group, and (b) said linker and said bulky group are connected via a second linkage group selected, independently, from an amine, amide, hydrazide, or thioether linkage; and wherein said condition is selected from, e.g., eczema, dermatitis, allergic rhinitis, Sjogren's disease, rheumatoid arthritis, psoriasis.



See, e.g., Example 10, page 37, Figure 11). Rothbard et al. teach at cols. 28-29 that conjugated glucocorticoids such as hydrocortisone, prednisone and prednisolone are used to treat eczema (including atopic dermatitis, contact dermatitis, allergic dermatitis), exfoliative dermatitis, lupus, allergic rhinitis (col. 24), Sjogren's disease (col. 31), rheumatoid arthritis (col. 29) and the like. The limitation "said corticosteroid conjugate (i) having anti-inflammatory activity in vivo (col. 24), (ii) having reduced activity in the central nervous system in comparison to said corticosteroid without said group, and (iii)

being resistant to in vivo cleavage, such that in vivo less than 10% of the administered corticosteroid conjugate is cleaved, separating said corticosteroid from said group, prior to excretion" necessarily reads upon the compounds taught by Rothbard et al. because the compounds taught (e.g., Example 10, pages 37, Figure 11) anticipate every single structural limitation in the claim as set forth above. The limitation "polyguanidino" is taught, e.g., in claims 12-14 of Rothbard et al., which teaches 5-25 subunits of guanidino molecules (see also col. 12) in the delivery-enhancing conjugates. See also claims 1, 61, 62, drawn to specific linkers for the conjugates and cols. 17-23 for linkers which encompass amino, amide, thiol. The limitation "rheumatoid arthritis" is taught, e.g., in col. 29, lines 51-55. With regards to half life, cols 18-19 teach that it may take up to 24 hours for half the administered compound to dissociate in vivo. Therefore, the reference is deemed to anticipate the claims above, as drafted.

***Conclusion***

No claim is allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARCELA M. CORDERO GARCIA whose telephone number is (571)272-2939. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia J. Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Cecilia Tsang/
Supervisory Patent Examiner, Art Unit 1654

/Marcela M Cordero Garcia/
Examiner, Art Unit 1654

MMCG 04/09